FUNCTIONAL GENOMICS STUDY TO UNDERSTAND THE ROLE OF SEROTONIN IN MOUSE EMBRYONIC STEM CELLS

Anusha Nagari

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Master's Thesis Committee

_____
Narayanan B. Perumal, Ph.D., Chair

_____
Mitradas M. Panicker, Ph.D.

_____
Yaoqi Zhou, Ph.D.

_____
Meeta Pradhan, Ph.D.

Dedicated to my family

TABLE OF CONTENTS

Page

LIST OF TABLES

LIST OF FIGURES

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ABSTRACT

FUNCTIONAL GENOMICS STUDY TO UNDERSTAND THE ROLE OF SEROTONIN IN MOUSE EMBRYONIC STEM CELLS

Serotonin (5-hydroxytryptamine, 5-HT) is a monoamine neurotransmitter that is synthesized from the amino acid L-tryptophan and is reported to localize in mitochondria of embryonic stem cells. Even before its role as a neurotransmitter in mature brain was discovered, 5-HT has been shown to play an important role in regulating brain development. However, there is a lack of knowledge about the downstream target genes regulated by serotonin in embryonic stem (ES) cells. Towards this end, our study helps in understanding transcriptional regulatory mechanisms of 5-HT responsive genes in ES cells. By combining the gene expression data with motif prediction algorithms, literature validation and comparison with public domain data, gene targets specific to endogenous or exogenous 5-HT in ES cells were identified. By performing one-way ANOVA, and volcano plots using GeneSpring software, we identified 44 5-HT induced and 29 5-HT suppressed genes, likely to be transcriptionally regulated by 4 & 2 TFs respectively. Motif enrichment analysis on these target genes using MotifScanner revealed that the transcription factor TFAP2A plays a key role in regulating the expression of 5-HT responsive genes. Furthermore, by comparing our dataset with published expression profiles of ES cells, we observed a number of 5-HT responsive target genes showing enrichment in ES cells. Genes such as Nanog, Slc38a5, Hoxb1 and Eif2s1 from this analysis have been observed to be components of 'stemness' phenotypes reported in literature. Functional annotation of the 5-HT responsive genes identified gene ontologies such as regulation of translation in response to stress and energy derivation by oxidation, suggesting a regulatory role for 5-HT in mitochondrial functions of ES cells. Additionally, enrichment of other biological process terms such as development of various parts of nervous system, cell adhesion, and apoptosis suggests that 5-HT target genes may play an important role in ES cell differentiation. Our study implemented a new combinatorial approach for identifying gene regulatory mechanisms involved in 5-HT responsive genes and proposed potential mediatory role for serotonin in ES cell differentiation and growth. Thus, this study provides potential 5-HT target genes in ES cells for biological validation.